



## **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV**

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### Key Considerations When Caring for Older Persons With HIV

- Antiretroviral therapy (ART) is recommended for all people with HIV regardless of CD4 T lymphocyte cell count **(AI)**. ART is especially important for older individuals because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART.
- Given that the burden of aging-related diseases is significantly higher among persons with HIV than in the general population, additional medical and social services may be required to effectively manage both HIV and comorbid conditions.
- Adverse drug events from ART and concomitant drugs may occur more frequently in older persons with HIV than in younger individuals with HIV. Therefore, the bone, kidney, metabolic, cardiovascular, cognitive, and liver health of older individuals with HIV should be monitored closely.
- Polypharmacy is common in older persons with HIV; therefore, there is a greater risk of drug-drug interactions between antiretroviral drugs and concomitant medications. Potential for drug-drug interactions should be assessed regularly, especially when starting or switching ART and concomitant medications.
- The decline in neurocognitive function with aging is faster in people with HIV than in people without HIV. HIV-associated neurocognitive disorder (HAND) is associated with reduced adherence to therapy and poorer health outcomes including increased risk of death. For persons with progressively worsening symptoms of HAND, referral to a neurologist for evaluation and management or a neuropsychologist for formal neurocognitive testing may be warranted **(BIII)**.
- Mental health disorders are a growing concern in aging people with HIV. A heightened risk of mood disorders including anxiety and depression has been observed in this population. Screening for depression and management of mental health issues are critical in caring for persons with HIV.
- HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older persons with HIV and complex comorbidities.
- Early diagnosis of HIV and counseling to prevent secondary transmission of HIV remains an important aspect of the care of older people with HIV

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

## Introduction

Effective antiretroviral therapy (ART) has increased survival in individuals with HIV,<sup>1,2</sup> resulting in an increasing number of older individuals living with HIV. In the United States, from 2012 through 2017, the annual fraction of persons newly diagnosed with HIV aged  $\geq 50$  years was stably 17%.<sup>3</sup> Among persons with HIV at year-end 2016, 48% were aged  $\geq 50$  years, 8% were aged  $\geq 65$  years, and trends suggest that these proportions will increase steadily.<sup>3</sup> Care of people with HIV will increasingly involve adults aged  $\geq 60$  years, a population for which data from clinical trials or pharmacokinetic (PK) studies are very limited. The discussion in this section of the guidelines refers to individuals aged  $\geq 50$  years as older persons with HIV.

There are several distinct areas of concern regarding aging and HIV.<sup>4</sup> First, older persons with HIV may suffer from aging-related comorbid illnesses and require substantially more non-ART medications<sup>5</sup> than younger people, which may complicate HIV clinical care.<sup>6</sup> Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of clinical syndromes generally associated with more advanced age. Third, reduced mucosal and immunologic defenses (e.g., postmenopausal atrophic vaginitis) and changes in risk related-behaviors (e.g., decrease in condom use because of less concern about pregnancy or more high-risk sexual activity with increased use of erectile dysfunction drugs) in older adults may lead to increased risk of acquisition and transmission of HIV.<sup>7,8</sup> Finally, HIV screening among older adults remains low because they are generally perceived to be at low risk of acquiring HIV.

## ***HIV Screening and Diagnosis in the Older Person***

Failure to consider a diagnosis of HIV has likely contributed to later initiation of ART in older persons with HIV.<sup>9</sup> The Centers for Disease Control and Prevention (CDC) estimates that in 2016, 36% of adults aged ≥55 years met the case definition for AIDS at the time of HIV diagnosis. The comparable CDC estimates are 16% for adults aged 25 to 34 years and 27% for adults aged 35 to 44 years.<sup>10</sup> In one observational cohort, older people (defined as those aged ≥35 years) appeared to have lower CD4 T lymphocyte (CD4) cell counts at seroconversion and steeper CD4 count decline over time,<sup>11</sup> and tended to present to care with significantly lower CD4 counts.<sup>12</sup> When individuals aged >50 years present with severe illnesses, HIV and AIDS-related opportunistic infections (OIs) need to be considered in the differential diagnosis of the illness.

Although many older individuals engage in risk behaviors associated with acquisition of HIV, they may see themselves or be perceived by providers as at low risk of infection and, as a result, they are less likely to be tested for HIV infection than younger persons.<sup>13,14</sup> Despite CDC guidelines recommending HIV testing at least once for individuals aged 13 to 64 years, and more frequently for those at risk,<sup>15</sup> HIV testing prevalence remains low (<5%) among adults aged 50 to 64 years, and decreases with increasing age.<sup>16</sup> Clinicians must be attuned to the possibility of HIV infection in older adults, including those aged ≥64 years, especially in those who may engage in high-risk behaviors. Sexual history taking and screening for other risk factors (e.g., injection drug use) that may place older adults at risk of HIV infection are therefore an important component of general health management for older adults. Risk-reduction counseling, and screening for HIV and sexually transmitted infections should be done, if indicated. Older adults who are at risk of acquiring HIV should be counseled on comprehensive HIV prevention strategies, including the option of HIV pre-exposure prophylaxis (PrEP). Age alone should not exclude older adults from being evaluated for and offered PrEP (refer to [CDC PrEP Guidelines](#) for details).

## ***Impact of Age on HIV Disease Progression***

HIV infection in older persons presents unique challenges and these challenges may be compounded by ART:

- Chronic HIV infection is associated with elevated cellular and soluble markers of immune activation and inflammation. Although these levels decline with ART, they remain higher than normal, even with suppressive ART. Levels of these markers also increase with aging, and the rate of this age-related change was demonstrated to be faster in people with HIV with viremia than in those with virologic suppression on ART and in people without HIV.<sup>17</sup>
- HIV infection may induce immuno-phenotypic changes akin to accelerated aging, with senescent T cells which in older persons have been associated with negative outcomes including frailty and cardiovascular disease.<sup>4,18-21</sup> Some studies have shown that people with HIV may exhibit chromosomal and immunologic features similar to those induced by aging, such as the accumulation of highly differentiated CD28<sup>-</sup>/CD57<sup>+</sup> CD8<sup>+</sup> T cells commonly used as markers of immunosenescence.<sup>22-24</sup> However, other studies show the immunologic changes in HIV to be distinct from age-related changes.<sup>25</sup> Cytomegalovirus (CMV) infection is very prevalent among people with HIV, and as they age, immune response to CMV—rather than HIV—may play a pivotal role in immunosenescence observed even in people with virologic suppression.<sup>26</sup>
- Although data on the increased incidence and prevalence of age-associated comorbidities in people with HIV are accumulating,<sup>27,28</sup> the age at diagnosis for myocardial infarction, stroke, and non-AIDS cancers in people with and without HIV is the same.<sup>28,29</sup>
- As the life expectancy of persons living with HIV increases with ART, more cisgender women with HIV are experiencing menopause. Although menopause may occur earlier in cisgender women with HIV than in cisgender women in the general population,<sup>30</sup> early menopause may also be a consequence of smoking, depression, substance use, and other psychosocial factors that are disproportionately present in cisgender women with HIV.<sup>31</sup>

- Older persons with HIV have a greater incidence of health complications and comorbidities than adults of a similar age who do not have HIV, and may exhibit a frailty phenotype (defined clinically as a decrease in muscle mass, weight, physical strength, energy, and physical activity) **earlier and in greater proportions than the general population.**<sup>32,33</sup> **Frailty in persons with HIV has been associated with adverse outcomes including incident cardiovascular disease, diabetes mellitus, recurrent falls and fractures, lower quality of life scores, cognitive impairment, hospitalization, and mortality.**<sup>34-43</sup> **Cisgender women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.**<sup>34,44-46</sup> **Although the frailty phenotype is still incompletely characterized in people with HIV, its early recognition may lead to targeted interventions to improve the wellbeing of this population.**<sup>43</sup>

## ***Antiretroviral Therapy in the Older Person with HIV***

### **Importance of Early Treatment Initiation**

ART is recommended for all individuals with HIV (AI; see [Initiation of Antiretroviral Therapy](#)). Early treatment may be particularly important in older adults in part because of decreased immune recovery and increased risk of serious non-AIDS events in this population.<sup>47,48</sup> In a modeling study based on data from an observational cohort, the beneficial effects of early ART were projected to be greatest in the oldest age group (people aged 45 to 65 years).<sup>49</sup> **This was demonstrated in an analysis of HIV cohorts from Europe and the Americas showing a lower all-cause and non-AIDS mortality with immediate ART initiation in people aged 50 to 70 years.**<sup>50</sup> **It was also seen in a START substudy in which persons aged >50 years were among the groups that experienced the greatest risk reduction when ART was started when CD4 counts were >500 cells/mm<sup>3</sup>.**<sup>51</sup> **All older persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) at <200 copies/mL with ART improves overall health and prevents sexual transmission of HIV.**

### **Choice of Antiretroviral Regimens in the Older Person with HIV**

The choice of antiretroviral (ARV) regimen for an older person with HIV should be informed by a comprehensive review of the person's other medical conditions and medications. The What to Start section ([Table 7](#)) of these guidelines provides guidance on selecting an ARV regimen based on a person's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease, osteoporosis). In older persons with HIV and reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see [Appendix B, Table 10](#)). In addition, ARV regimen selection may be influenced by potential interactions between ARV medications and drugs used concomitantly to manage comorbidities (see [Tables 21a-22b](#)). Adults aged >50 years should be monitored for ART effectiveness and safety as similarly recommended for other populations with HIV (see [Table 3](#)); however, in older persons, special attention should be paid to the greater potential for adverse effects of ART on renal, liver, cardiovascular, central nervous system, metabolic, and bone health (see [Table 17](#)). **ART regimens that contain tenofovir disoproxil fumarate (TDF), boosted protease inhibitors (PIs), or both are associated with a significantly greater loss of bone mineral density than regimens containing other NRTIs and integrase strand transfer inhibitors (INSTIs).**<sup>52-55</sup> **Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide may be considered as alternatives to the use of TDF in older individuals who may be at risk of osteopenia or osteoporosis; however, with ABC, the benefit should be balanced with potentially increasing risk of cardiovascular disease.**

### **Antiretroviral Efficacy and Safety Considerations in the Older Person with HIV**

The efficacy, PKs, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically. There is no evidence that the virologic response to ART differs in older and younger people. In an observational study, a higher rate of viral suppression was seen in people aged >55 years than in younger people.<sup>56</sup> However, ART-associated CD4 cell recovery in older adults is generally slower and

lower in magnitude than in younger people;<sup>12,57-59</sup> suggesting that starting ART at a younger age may result in better immunologic response and possibly clinical outcomes.

Hepatic metabolism and renal elimination are the major routes of drug clearance, including the clearance of ARV drugs. Both liver and kidney functions decrease with age and may result in impaired drug elimination and increased drug exposure.<sup>60</sup> Most clinical trials have included only a small proportion of participants aged >50 years, and current ARV dosing recommendations are based on PK and pharmacodynamic data derived from participants with normal organ function. Because it is unknown whether drug accumulation in the older person may lead to greater incidence and severity of adverse effects than seen in younger persons, therapy in older persons requires close monitoring and heightened awareness of drug-related adverse outcomes.

### ***Impact of Comorbidities and Polypharmacy in Older Persons with HIV***

People with HIV and aging-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management.<sup>5</sup> In addition to taking medications to manage HIV infection and comorbid conditions, many older persons with HIV are also taking medications to relieve discomfort (e.g., pain medications, sedatives) or to manage adverse effects of medications (e.g., anti-emetics). Older individuals may also self-medicate with over-the-counter medicines or supplements.

Polypharmacy is more common in older persons with HIV than similarly aged persons in the general population.<sup>5,61-63</sup> In one large cohort of older patients with HIV in France, 62% of those whose HIV was diagnosed before 2000 had one or more comorbidities, and 70% were receiving at least one comedication.<sup>64</sup> Among persons living with HIV aged ≥65 years, the prevalence of comorbidities and polypharmacy rose with increasing age and duration of HIV infection.<sup>65</sup>

In older persons without HIV, polypharmacy is a major cause of iatrogenic complications.<sup>66</sup> Some of these complications may be caused by medication errors (by prescribers or patients), medication nonadherence, additive drug toxicities, and drug-drug interactions. Older persons with HIV are probably at an even greater risk of polypharmacy-related adverse consequences than younger or similarly aged people without HIV. When evaluating any new clinical complaint or laboratory abnormality in people with HIV, especially in older persons, clinicians should always consider the possible role of adverse drug reactions from both ARV drugs and other concomitantly administered medications.

### **Drug-Drug Interaction Concerns**

Drug-drug interactions are common with ART and can be easily overlooked by prescribers.<sup>67</sup> Potential drug-drug interactions can occur between ARV and non-ARV medications, as well as between non-ARV medications.<sup>63</sup> The available drug interaction information on ARV agents is derived primarily from PK studies performed in small numbers of relatively young participants with normal organ function who do not have HIV (see Tables 21a-22b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of an interaction may be greater in older persons with HIV than in younger people with HIV; therefore, it is very important to remain vigilant to potential drug-drug interactions given the high prevalence of polypharmacy in older persons with HIV. In reviews of ARV and non-ARV medications prescribed for older persons with HIV, more than half of the medications had the potential for drug-drug interaction, including some severe interactions.<sup>68,69</sup> The risk is higher with PI-based ART than with INSTI-based ART.<sup>68-70</sup>

### **Adherence Concerns**

Suboptimal adherence to ART is the most common cause of treatment failure. Complex dosing requirements, high pill burden, polypharmacy, inability to access medications because of cost or availability, limited health literacy (including misunderstanding of instructions), depression, and neurocognitive impairment are among the key reasons for nonadherence.<sup>71</sup> Although many of these factors associated with nonadherence



may be more prevalent in older persons with HIV, some studies have shown better adherence to ART among older persons than younger individuals.<sup>72-74</sup> Severe menopausal symptoms are also associated with reduced adherence to ART, which increases the risk of drug resistance and adverse HIV-related health outcomes in menopausal cisgender women.<sup>75</sup> Clinicians should regularly engage with older persons to identify any factors, such as neurocognitive deficits or hormonal changes, that may decrease adherence to ART. To facilitate medication adherence, it may be useful to discontinue unnecessary medications, simplify regimens, and recommend evidence-based behavioral approaches including the use of adherence aids such as pillboxes or daily calendars, and support from family members (see [Adherence to the Continuum of Care](#)).

### Optimizing Antiretroviral Therapy in Older Persons with HIV

Given the greater incidence of comorbidities, non-AIDS complications, and frailty among older people with HIV, switching one or more ARVs in an HIV regimen may be necessary to minimize toxicities and drug-drug interactions. For example, expert guidance now recommends bone density monitoring in men aged  $\geq 50$  years and postmenopausal cisgender women, and suggests switching from TDF or boosted PIs to other ARVs in older persons at high risk for fragility fractures.<sup>76</sup> Given the high prevalence and faster progression of chronic kidney disease in aging persons with HIV, likely from a combination of HIV, ART, and non-HIV risk factors, development of the disease in an older person on ART must be monitored with great vigilance.<sup>77,78</sup> In persons with HIV at risk for or with declining renal function, consideration should be given to avoiding regimens containing TDF and atazanavir.<sup>79</sup>

### Interrupting or Discontinuing Antiretroviral Therapy in Older Persons with HIV

Few data exist on the use of ART in severely debilitated people with chronic, severe, or non-AIDS-related terminal conditions.<sup>80,81</sup> Withdrawal of ART usually results in rebound viremia and a decline in CD4 count. In addition, an acute retroviral syndrome after abrupt discontinuation of ART has been reported. Even in severely debilitated adults, most clinicians would continue therapy if there are no significant adverse reactions to the ARV drugs. In cases where ART negatively affects quality of life, the decision to continue therapy should be made together with the patient and/or family members after a discussion of the risks and benefits of continuing or withdrawing treatment.

### *Non-AIDS HIV-Related Complications and Other Comorbidities in the Older Person with HIV*

As AIDS-related morbidity and mortality have decreased among persons treated effectively with ART, non-AIDS conditions constitute an increasing proportion of serious illnesses among people with HIV.<sup>82-84</sup> The burden of age-related diseases is significantly higher among persons with HIV than in the general population, likely due to both traditional non-HIV-related and HIV-related factors.<sup>85</sup> Heart disease and cancer are the leading causes of death in older Americans.<sup>86</sup> Similarly, other non-AIDS events such as cognitive impairment, and liver disease have also emerged as major causes of morbidity and mortality in people with HIV receiving effective ART. Moreover, people with HIV are more likely to be current or former cigarette smokers than adults without HIV,<sup>87</sup> and model-based analyses have suggested that smoking cessation could improve life expectancy among older adults with HIV on ART.<sup>88</sup>

The prevalence of multimorbidity among persons with HIV has increased in the past decade,<sup>89</sup> with hypertension and hypercholesterolemia being the most common comorbidities. The presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection may add to the disease burden of aging among adults with HIV.<sup>90-92</sup>

HIV-specific primary care guidelines have been developed and are available for clinicians caring for older persons with HIV.<sup>93,94</sup> Specific guidelines have also been developed for the evaluation and management of the following specific comorbidities in people with HIV: bone health,<sup>76</sup> kidney disease,<sup>95</sup> and cardiovascular disease.<sup>96</sup> In addition, the following guidelines recently developed for the general population can be applied

to the older persons with HIV: management of [hyperglycemia](#)<sup>97</sup> and [hyperlipidemia](#).<sup>98</sup> However, it is important to note that the recommendations in these guidelines have not all been validated in the context of HIV disease. For instance, cardiovascular risk prediction functions developed for the general population likely underestimate the risk in persons with HIV.<sup>99</sup>

### *Neurocognitive Impairment and Mental Health Concerns in the Older Person with HIV*

HIV-associated neurocognitive disorder (HAND), manifesting as difficulty with memory, attention, speed of information processing, and executive and motor functions, affects up to 30% of people with HIV on virally suppressive ART.<sup>100</sup> Though an accurate prevalence of neurocognitive impairment in older people with HIV is not yet available, the risk of HIV-associated brain injury and HAND appears to be higher with increasing age.<sup>101-103</sup> Neurocognitive function declines with increasing age in people with or without HIV, but the trajectory of the decline is steeper in individuals with HIV.<sup>104</sup> This accelerated decline is likely multifactorial, relating to injury associated with direct HIV effects in the brain, higher prevalence of comorbidities and coinfections, more severe vascular disease, mental health disorders, social isolation, and polypharmacy in this population.<sup>105-107</sup> Hormonal shifts that occur with aging may contribute to neurocognitive impairment, and these changes may manifest as unique differences in clinical manifestations by gender.<sup>108</sup> Finally, the risk of neurodegenerative disease rises with increasing age independent of HIV, and differentiating HAND from Alzheimer's disease or other forms of progressive dementia is now an important clinical concern.<sup>109</sup>

HAND carries potentially detrimental clinical consequences for aging people with HIV. In a prospective observational study, neurocognitive impairment was predictive of lower likelihood of retention in care among older persons.<sup>110</sup> HAND is also associated with reduced adherence to therapy<sup>111</sup> and poorer health outcomes including increased mortality.<sup>112</sup> Given the importance of cognitive health, screening for neurocognitive impairment is important, though optimal primary-care based screening methods are as yet unclear. Initial screening with questions regarding any symptoms of memory or concentration difficulties should be performed routinely, though individuals with substantial impairment may not have enough insight into their condition to answer the questions. No brief cognitive screening test has been clearly shown to be sensitive or specific for HAND; the frequently used Mini-Mental State Exam does not typically capture executive function impairment which is the main manifestation of subtle HAND.<sup>113</sup> The Montreal Cognitive Assessment may be more sensitive for HAND but is not specific. If a patient has persistent concerns over time, has symptoms corroborated by an acquaintance, or has progressively worsening symptoms, referral to a neurologist for evaluation and management or to a neuropsychologist for formal neuropsychological testing may be warranted (**BIII**).

Mental health disorders are a growing concern in aging people with HIV, though little is known about their prevalence and consequences in this population specifically. In a study that compared a cohort of individuals aged >60 years with HIV to a historical control group of healthy older individuals, a heightened risk of mood disorders including anxiety and depression was noted among those with HIV.<sup>114</sup> Social isolation combined with depression is particularly common among older adults with HIV and, in addition to its direct effects on morbidity and mortality, may contribute to poor medication adherence and retention in care.<sup>115,116</sup> The risk of suicide remains greater in people with HIV than in the general population, though increasing age may not further heighten the risk.<sup>117</sup> Screening for depression and management of mental health issues are critical aspects of HIV primary care; guidelines for people with HIV, as well as for aging individuals without HIV, recommend behavioral approaches including individual psychotherapy, cognitive behavioral therapy, and group therapy, and often pharmacological treatment.<sup>118,119</sup> Integrated care models with routine screening by health care support staff, review by primary providers, and referral to on-site mental health specialists are likely to be the most effective approaches in vulnerable aging populations.

### **Health Care Utilization, Cost Sharing, and End-of-Life Issues**

The significantly increased burden of age-related comorbidities, including cardiovascular disease, chronic kidney disease, neurocognitive disease, and fractures, leads to a considerable increase in healthcare

utilization and higher costs.<sup>120</sup> Out-of-pocket health care expenses (e.g., copayments, deductibles), loss of employment, and other financial-related factors can cause temporary interruptions in treatment, including ART, which should be avoided whenever possible. The increased life expectancy and higher prevalence of chronic complications in aging populations with HIV can place greater demands upon HIV services<sup>121</sup> and require a focused approach to prioritize modifiable health-related problems.<sup>122</sup> Facilitating continued access to insurance can minimize treatment interruptions and reduce the need for other services to manage concomitant chronic disorders. As with all aging people, it is important to discuss living wills, advance directives, and long-term care planning.

## Conclusion

HIV infection can be overlooked in aging adults who tend to present with more advanced disease and experience accelerated CD4 loss. HIV induces immune-phenotypic changes that have been compared to accelerated aging. Effective ART has prolonged the life expectancy of people with HIV, increasing the number of adults aged >50 years living with HIV. However, unique challenges in this population include greater incidence of health complications and comorbidities, some of which may be exacerbated or accelerated by long-term use of some ARV drugs. Providing comprehensive multidisciplinary medical and psychosocial support to patients and their families (the “Medical Home” concept) is of paramount importance in the aging population. Continued involvement of HIV experts, geriatricians, and other specialists in the care of older persons with HIV is warranted.

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